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SUMMARY: This study investigated the relationship of acute lower respiratory illness (LRI) to level and change in level of forced expiratory volumes in a cohort of 801 children, followed longitudinally for a maximum of 13 yr. The co-occurrence of respiratory illness before 2 yr of age and two or more LRI during a single surveillance year was associated with a 20.3% lower mean cross-sectional level of FEF25-75, and with reduced longitudinal change in level of FEF25-75. The effect of LRI on lung function was uniformly stronger for boys than for girls. Of the children with illness before 2 yr of age and two or more LRI, six of 14 were male asthmatics with mean levels of FEF25-75 that were lower than those of other asthmatic children. Pneumonia and/or hospitalization for respiratory illnes prior to the onset of study were associated with lower cross-sectional levels of forced expiratory volumes at entry to the study, even when asthmatics/persistent wheezers were eliminated from the analysis (6.1% lower level of FEV1 for a nonasthmatic boy with previous hospitalization versus a nonasthmatic boy without hospitalization). In the longitudinal analysis, pneumonia and/or hospitalization were associated with slower increase in level of forced expiratory volumes, even after adjusting for "ever diagnosis of asthma/current any wheeze" (starting at the same level, after eight years a boy with hospitalization would develop a 5.0% lower FEV1 than a boy without hospitalization). Acute LRI also was evaluated as a predictor of chronic respiratory symptoms. A strong association was found between previous hopitalization and subsequent chronic cough (Odds Ratio [OR]= 3.8)/chronic phlegm (OR= 7.1) at entry to the study; eight years later, smoking was the only significant predictor of these symptoms, and no hospitalized child had taken up smoking. Future studies may enable us to explore interactions between severe respiratory illness in early childhood and the effect of cigarette smoke or indoor/outdoor air pollution.

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Acute Lower Respiratory Illness in Childhood as a Predictor of Lung Function and Chronic Respiratory Symptoms[1-3]

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SUMMARY This study investigated the relationship of acute lower respiratory illness (LRI) to level and change in level of forced expiratory volumes in a cohort of 801 children, followed longitudinally for a maximum of 13 yr. The co-occurrence of respiratory illness before 2 yr of age and two or more LRI during a single surveillance year was associated with a 20.3% lower mean cross-sectional level of FEF_{25-75}, and with reduced longitudinal change in level of FEF_{25-75}. The effect of LRI on lung function was uniformly stronger for boys than for girls. Of the children with illness before 2 yr of age and two or more LRI, six of 14 were male asthmatics with mean levels of FEF_{25-75} that were lower than those of other asthmatic children. Pneumonia and/or hospitalization for respiratory illness prior to the onset of study were associated with lower cross-sectional levels of forced expiratory volumes at entry to the study, even when asthmatics/persistent wheezers were eliminated from the analysis (6.1% lower level of FEV, for a nonasthmatic boy with previous hospitalization versus a nonasthmatic boy without hospitalization). In the longitudinal analysis, pneumonia and/or hospitalization were associated with slower increase in level of forced expiratory volumes, even after adjusting for "ever diagnosis of asthma/current any wheeze" (starting at the same level, after eight years a boy with hospitalization would develop a 5.0% lower FEV, than a boy without hospitalization). Acute LRI also was evaluated as a predictor of chronic respiratory symptoms. A strong association was found between previous hospitalization and subsequent chronic cough (Odds Ratio[OR] = 3.8)/chronic phlegm (OR = 7.1) at entry to the study; eight years later, smoking was the only significant predictor of these symptoms, and no hospitalized child had taken up smoking. Future studies may enable us to explore interactions between severe respiratory illness in early childhood and the effect of cigarette smoke or indoor/outdoor air pollution.

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Introduction

Acute lower respiratory illness (LRI) in early childhood has been proposed as a risk factor, independent of the effect of cigarette smoke, for lower level and slower growth of lung function in later childhood and for faster decline of lung function in adulthood (1, 2). Because wheeze is often a manifestation of an acute LRI in childhood whether or not a child has asthma, separation of the effects of asthma and other acute respiratory illnesses (infections) on level and growth of lung function in children is complicated. Asthma or bronchial responsiveness may alter level and change in level of lung function or predispose to increased severity of LRI, and may account for the association of LRI with alterations in lung function development. Severe infection in early childhood may, on the other hand, alter the course of asthma or predispose towards bronchial responsiveness and its subsequent effects on lung function.

As part of a longitudinal, population-based study of early-life risk predictors for chronic obstructive lung disease in adult life, the relationship between lung function and several measures of acute LRI in childhood was investigated. The results suggest that in the population studied, only the more severe acute LRI, particularly those requiring hospitalization, may be associated independently with subsequent lower level and slower growth of lung function in children.

Methods

The details of the initial selection and screening of the population have been published previously (3-5). A 34% random sample was selected from all children 4 to 10 yr of age in the public and parochial schools of East Boston, Massachusetts, as of September 1974. Between January and June 1975, interviewers visited the households of the index children who had been selected. They enumerated all residents of the households, and these residents, plus the index children, constituted the initial study population. All available members of the cohort have been screened on an annual basis since 1975, except for the second and third screenings, which were limited to the index children as part of a special study to assess prospectively their acute respiratory illness experience.

Standardized questionnaires were used to obtain baseline histories of respiratory symptoms and illnesses, as well as smoking histories and demographic data. Parents answered the questionnaire for children 10 yr of age and younger, except those questions that pertained to the child's smoking history; all others answered for themselves.

The acute respiratory illness experience for the index children in the 5- to 11-yr-old category as of September 1975 was then assessed prospectively over a 2-yr period (6). Parents of the children were contacted by telephone every 2 wk (except in July and August) from September 1975 through June 1977; a brief questionnaire about illness symptoms was administered. Children who experienced one or more selected respiratory symptoms for two days or more in the previous 2 wk were visited in their homes, and a more detailed history of their respiratory symptoms was obtained by an interviewer-administered questionnaire. Acute lower respiratory illness was defined as acute symptoms of phlegm from the chest or pleuritic chest pain with or without wheeze that lasted 48 h or more. Wheeze alone was not considered an adequate criterion for an acute LRI.

Subjects performed forced vital capacity (FVC) maneuvers annually with the use of an 8-L water-filled, portable recording spirometer (Survey Spirometer; Warren Collins, Braintree, MA) while in the sitting position and without the use of a noseclip. The maximum value for each measure of lung func-

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tion was obtained from values derived from five acceptable tracings. Standard criteria for curve acceptability and flow measurements were used. All lung function measurements were corrected to BTPS and were converted into percent predicted values with the nomograms of Dickman and coworkers (7).

Data Analysis

Six measures of acute lower respiratory illness were considered as predictors of level and change in level of the maximum FEV_1, FVC, and FEF_{25-75}: (*1*) Acute LRI at Study Year 2; (*2*) Acute respiratory illness before 2 yr of age, defined as a parent's reporting that the child had had croup, bronchiolitis, bronchitis, or pneumonia, (*3*) Acute respiratory illness before age 2 yr combined with acute LRI at Study Year 2, (*4*) Pneumonia prior to entry into the study, as reported by the parent, (*5*) Hospitalization for respiratory illness prior to entry into the study, as reported by the parent, and (*6*) Pneumonia and hospitalization for respiratory illness prior to entry into the study.

For each of the measures of LRI experience, mean percent predicted lung function levels were plotted by examination year as an initial exploration of possible differences in level of lung function between groups with and without respiratory illness exposure. Standard methods of multiple linear regression were then applied to assess measures of prestudy LRI experience (illness before 2 yr of age, pneumonia, or hospitalization), as predictors of level of lung function at entry to the study. Acute LRI experience reported during Study Year 2 was considered as a predictor of level of lung function in the subsequent year. Cross-sectional multiple linear analyses were adjusted for maternal smoking, but not for personal smoking, because there were no subjects with adequate data for the analyses who smoked in the years under consideration (Study Years 1 to 3). Pulmonary function and height were expressed in natural logarithms in cross-sectional analyses to stabilize the variance of the residuals. Because in the cross-sectional analyses lung function was expressed in natural logarithms, the partial regression coefficients or "parameter estimates" express the adjusted logarithmic difference in lung function between those exposed and those not exposed to a particular covariate. Thus, the "parameter estimates" express the adjusted ratio of lung function of those exposed to those unexposed to a particular covariate.

The association between each of the six measures of acute lower respiratory illness experience and change in level of lung function, measured over a maximum of 13 yr, was assessed with a Markov-type autoregressive model. Details of the autoregressive model and its application to assessment of change in lung function of children have been previously published (5, 8). Level of lung function (FEV_1, FEF_{25-75}, or FVC) at any given survey was considered as a function of mean level of lung function at the previous survey, age in years at the current survey, sex, height, change in height over 1-yr intervals, an interaction between height and age; and an interaction between sex and age. For the purposes of presentation of results of longitudinal models, these factors are called "growth factors." Level of lung function also was considered as a function of personal smoking status and mother's smoking status at the previous survey. For each child, only pairs of data spaced one year apart were used. While this approach to longitudinal data analysis is considered relatively efficient, it does result in nonutilization of non-equidistant data points. Continuous variables, other than the dependent variable, were centered around their median values. As in the cross-sectional analyses, pulmonary function and height were expressed as natural logarithms. The "parameter estimates" in the longitudinal models, when exponentiated, made it possible to project the adjusted ratio of lung function of an exposed subject to the lung function of a subject unexposed to a particular covariate, after a given period of time, assuming that the subjects started at the same level of function (5, 7) (*see* table 3 for a specific example).

Examination of the distribution of residuals (observed-predicted values) was used to assess the goodness of fit of the model in relation to height, age, and previous level of lung function. The stability of the parameter estimate of interest was assessed by an examination of the distribution of parameter estimates obtained by multiple fittings of the model. Each time the model was fit, all the data points from one subject were eliminated.

Separate analyses were performed to assess whether any of the six measures of acute lower respiratory illness experience had an effect on change in level of lung function independent of the effect of these other variables that had been previously established to effect change in level of lung function (5, 9, 10). Analyses were performed with and without children with doctor's diagnosis of asthma or mother's report of child's persistent wheeze at entry to the study; also with and without adjustment for "ever diagnosis of asthma," if there was a current report of any wheeze. To examine whether there were sex-specific effects of acute LRI on lung function, sex-stratified models also were examined.

Although analyses that assessed change in level of lung function are based on a maximum of 13 yr of data, the percent of the 801 children lost to follow-up increased considerably after Study Year 8 (up to Year 8 loss to follow-up averaged less than 3% per yr; for Years 8 to 12, loss to follow-up averaged 13% per yr). The number of boys with a history of hospitalization who continued to participate in the study was stable from Years 1 through 9. Over the subsequent four-year period, there was a 64% drop in participation of this subgroup from 25 to 9 boys. The autoregressive model, therefore, cannot be used with confidence to project beyond eight years what the differences in longitudinal change in level of lung function would be for two hypothetical children with and without early childhood acute LRI exposures.

Acute lower respiratory illness experience as a predictor of subsequent respiratory illness and symptoms also was evaluated. Hospitalization for respiratory illness prior to entry to the study was examined as a predictor of respiratory symptoms at entry to the study (t), at t + 5 yr, and at t + 8 yr. These time intervals were selected because beyond eight years sufficient data on symptoms were unavailable for the reason specified above.

For this analysis, persistent wheeze was defined as wheeze occurring most days or nights. Chronic cough was defined as cough on most days for as much as three months of the year; chronic phlegm as phlegm, sputum, or mucus from the chest on most days for as many as three months of the year. "Debilitating chest illness" was defined as chest illness that kept a child from his/her usual activities for as much as three days in a week.

Results

Characteristics of the Cohort

There were 421 index children and 380 siblings for a total of 801 children available for analysis. Analyses that assessed LRI in Study Year 2 as a predictor used only the subset of index children with acceptable data; all other analyses included the siblings. No systematic differences were seen between the children included versus those excluded from the various analyses because of missing data on one or another of the variables. Of the 801 index children and their siblings, 22.3% had had illness before age 2 yr, 13.5% had had pneumonia, and 8.6% had been hospitalized for respiratory illness prior to study onset. Of the index children studied during Year 2, 14.2% had two or more LRI during that year.

The indicators of LRI were correlated with each other and with a history of asthma and persistent wheeze. LRI at Study Year 2 was associated with illness before age 2 yr (OR = 2.0; 95% Confidence Interval [CI] = 1.0–4.3) and pneumonia (OR = 2.1; 95% CI = 0.9–4.8). Of the 421 index children, 7 of 29 (24.1%) children with a history of hospitalization for acute respiratory illness prior to entry to the study had ⩾ 2 LRI, whereas 43 of 320 (13.4%) of those not hospitalized had ⩾ 2 LRI.

Those children with a history of hospitalization prior to entry into the study (n = 69) were more likely to have had pneumonia (OR = 12.5; 95% CI = 7.0–22.3) and illness before age 2 yr (OR = 7.7; 95% CI = 4.2–14.3) that children who had not been hospitalized. They were also

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more likely to have entered the study with a doctor's diagnosis of asthma (OR = 9.9; 95% CI = 5.0–19.3). At entry into the study, 55% of the children with a history of hospitalization had pneumonia; 75.4% had illness before age 2 yr, and 30.4% had a doctor's diagnosis of asthma. In contrast, the prevalence of asthma in the nonhospitalized population was 4.2%. Eight years after entry to the study, of the children previously hospitalized, 35.5% had ever had a diagnosis of asthma, as compared to 10.7% of the children not hospitalized prior to entry to the study (OR = 4.6; 95% CI = 1.9–10.9).

Acute LRI as a Predictor of Lung Function

Cross-sectional level of FEV_1 at Study Year 3 was not lower for children with ⩾ 2 LRI during Study Year 2, after adjustment for the effects of age, height, sex, and maternal smoking (parameter estimate for LRI = −0.0211, p = 0.38). Among the children without asthma or persistent wheeze, there was also no association between level of FEF_{25-75} and ⩾ 2 LRI, although an association was suggested when the asthmatic children were included in the analysis (parameter estimate for LRI = −0.0903, p = 0.054).

An association was noted between lower cross-sectional level of FEF_{25-75} and having had *both* illness before age 2 yr and ⩾ 2 LRI at Study Year 2. Of the 14 children with this repeated LRI experience, only three had an FEF_{25-75} greater than 75% predicted at entry to the study. Only two of the children were girls; 12 (85%) were boys, six of whom had either a doctor's diagnosis of asthma or persistent wheeze on initial examination (table 1). For the boys, mean cross-sectional percent predicted levels of FEF_{25-75} were low both at entry to the study and for each of the subsequent 12 examination periods (figure 1). The subgroup of six boys with asthma or persistent wheeze who had both illness before age 2 yr and ⩾ 2 LRI also maintained mean levels of percent predicted FEF_{25-75} that were persistently lower than all other boys who at entry had asthma/persistent wheeze without the same history of LRI (n = 17 at Study Year 3; yearly data for mean FEF_{25-75} by subgroup not shown).

Adjusting for age, height, sex, and maternal smoking, the mean cross-sectional level of FEF_{25-75} at Study Year 3 was 20.3% lower (p = 0.003) for the children with both illness before 2 yr of age and ⩾ 2 LRI (n = 11 for those with sufficient data on all variables), than for all other children, and remained lower after adjusting additionally for asthma/persistent wheeze. Although differences were not significant, children with both illness before 2 yr of age and ⩾ 2 LRI also tended to have a higher FVC than other children. At Study Year 3, children with illness before age 2 yr but without ⩾ 2 LRI at Study Year 2 (n = 28) had adjusted cross-sectional levels of FEF_{25-75} similar to the levels of the children with no lower respiratory illness experience (n = 172) and the levels of the children with only ⩾ 2 LRI but no illness before 2 yr of age (n = 20). In the longitudinal analysis, no association was found between ⩾ 2 LRI at Study Year 2 and slower increase in level of FEV_1 or FEF_{25-75} (parameter estimate of LRI = 0.0034, p = 0.48; and −0.0044, p = 0.63 for FEV_1 and FEF_{25-75}, respectively), after adjustment for previous level of lung function, sex, age, height, their interactions, and smoking. These conclusions did not change if the longitudinal analyses were restricted to observations for children younger than 12 yr of age.

The increase in level of FEF_{25-75} was slower (parameter estimate = −0.0509, p = 0.006) for the children with both illness before 2 yr of age and ⩾ 2 LRI at Study Year 2, compared to the rest of the population; this association remained significant even after additional adjustment for "ever diagnosis of asthma and current any wheeze" and after restriction of the analysis to the boys alone. The increase in level of FVC, on the other hand, was significantly faster for the children with both illness before 2 yr of age and ⩾ 2 LRI (parameter estimate = 0.0262, p = 0.011); this association also remained significant after additional adjustment for "ever diagnosis of asthma and current any wheeze."

Illness before 2 yr of age, pneumonia prior to entry into the study, and hospitalization prior to entry into the study were evaluated as predictors of cross-sectional level and longitudinal increase in level of lung function for the entire cohort of 801 children. Mean cross-sectional levels of percent predicted FEF_{25-75} for boys (not girls) with illness before 2 yr of age tended to be lower throughout the 13 years of the study (figure 2). Mean levels of percent predicted FEV_1 for those boys (not girls) with illness before 2 yr of age were lower only in the first two examination years. Significant associations were found between illness before 2 yr of age and lower cross-sectional adjusted levels of FEV_1 and FEF_{25-75} on entry to the study only when children with asthma/persistent wheeze were included in the cross-sectional analyses (parameter estimate for FEF_{25-75}, including children with asthma/persistent wheeze = −0.06791, p = 0.05; parameter estimate excluding them = −0.0468, p = 0.16). Stratification by sex did not strengthen the associations of interest for the nonasthmatic children. Illness before 2 yr of age was not a significant predictor of longitudinal increase in level of FEV_1, FVC, or FEF_{25-75}, after adjustment for growth factors and smoking.

Of the children with asthma/persistent wheeze, a similar influence was found in relation to the cross-sectional association between pneumonia and a lower lung function level at entry to the study. Pneumonia was significant as a predictor of

TABLE 1

RELATIONSHIP BETWEEN ILLNESS BEFORE 2 YR OF AGE AND LOWER RESPIRATORY ILLNESS AT STUDY YEAR 2, STRATIFIED BY ASTHMA OR PERSISTENT WHEEZE AND BY SEX

	No Illness before 2 yr of Age (n)		Illness before 2 yr of Age (n)	
	0–1 LRI	⩾ 2 LRI	0–1 LRI	⩾ 2 LRI
Diagnosis of Asthma or Persistent Wheeze				
No				
Female	102	17	17	2
Male	124	14	22	6
Yes				
Female	9	1	4	0
Male	15	3	5	6
Total	250	35	48	14

Definition of abbreviation: LRI = lower respiratory illness.

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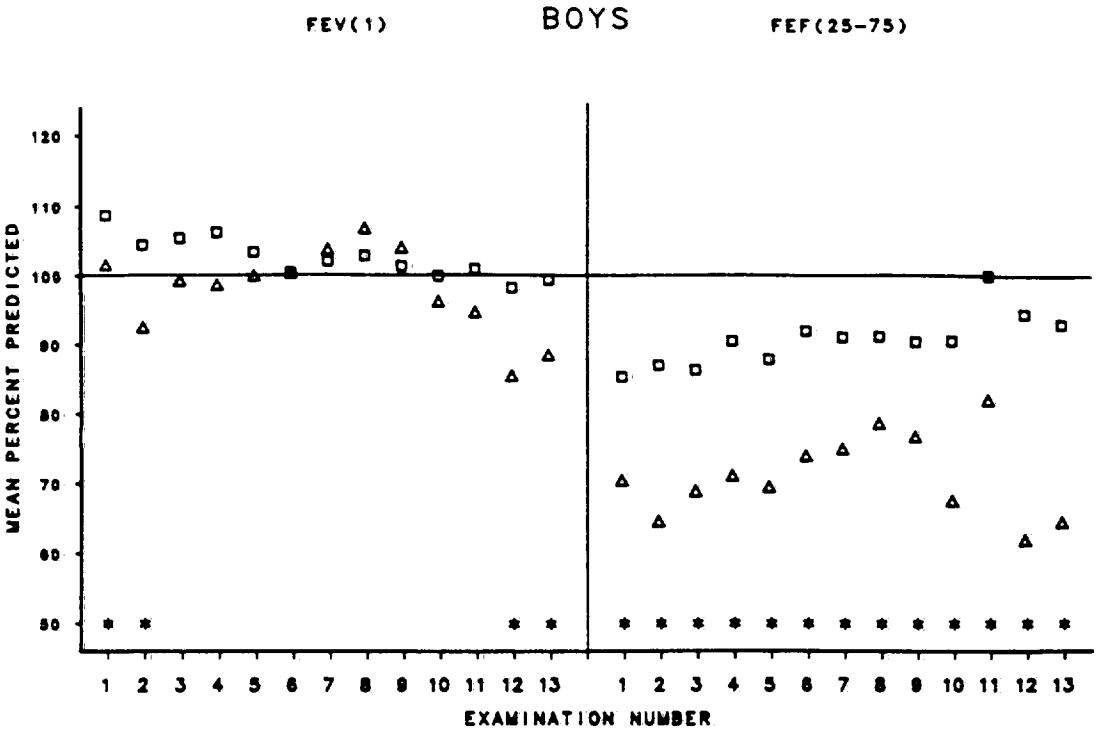

Fig. 1. Mean percent predicted FEV_1 and FEF_{25-75} at each annual examination (1 to 13) in index boys (n = 244) classified according to acute respiratory illness experience. Triangles = boys with both illness before 2 yr of age and also ≥ 2 lower respiratory illnesses at Study Year 2. Squares = all other boys (those without both illness before 2 yr of age and also ≥ 2 lower respiratory illnesses at Study Year 2). The asterisks represent pairs of values ± 1 SE that do not overlap.

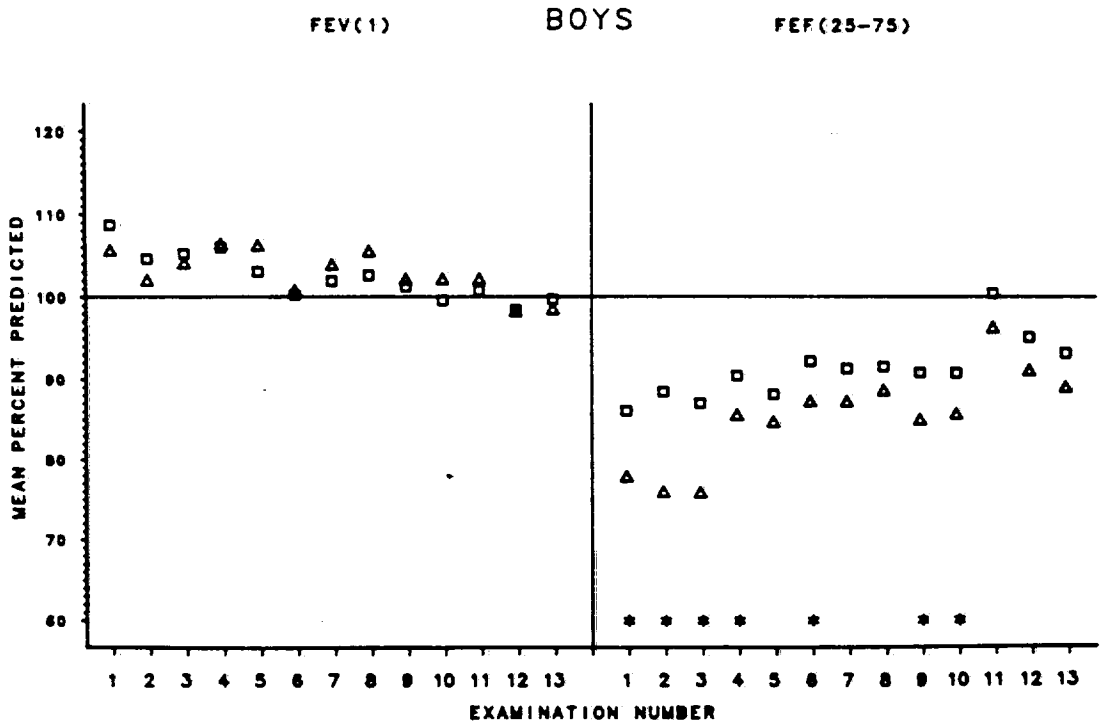

Fig. 2. Mean percent predicted FEV_1 and FEF_{25-75} at each annual examination (1 to 13) in boys (n = 422 and includes index boys and male siblings) classified according to presence or absence of history of illness before 2 yr of age (bronchitis, bronchiolitis, croup, or pneumonia). Triangles = boys with illness before 2 yr of age; squares = boys without illness before 2 yr of age. The asterisks represent pairs of values ± 1 SE that do not overlap.

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entry level of FEV_1 (parameter estimate = −0.0439, p = 0.02) in a regression model that included all children and adjusted for age, sex, height, and maternal smoking. In a sex-stratified model, a history of pneumonia was a significant predictor of lower level of FEV_1 for boys (parameter estimate = −0.0614, p = 0.018), but not for girls (parameter estimate = −0.0248, p = 0.38). When children with asthma/persistent wheeze were excluded from the models, there was a reduction in the strength of the association between pneumonia and lower initial level of FEV_1 for the entire cohort (parameter estimate = −0.0350, p = 0.10), and for boys alone (parameter estimate = −0.0440, p = 0.12).

In the longitudinal analysis, there was a significant association between a history of pneumonia and a slower rate of increase in level of FEF_{25-75} for boys, but not for girls. This association for boys remained after additional adjustment for "ever diagnosis of asthma/current any wheeze" (parameter estimate for pneumonia = −0.0252, p = 0.02).

Hospitalization for respiratory illness prior to entry to the study was the strongest predictor of cross-sectional level of lung function, independent of the influence of a history of asthma or persistent wheeze. Sex stratification demonstrated that a consistent pattern of lower mean percent predicted FEF_{25-75} was present for boys with a history of hospitalization (figure 3), but not for girls (figure not shown). In the first nine years of the study, boys with a history of hospitalization, but not girls, tended to have a lower mean percent predicted FEV_1.

At entry to the study, a history of hospitalization was associated with a level of FEV_1 that was lower than for children without a history of hospitalization (parameter estimate = −0.0654, p = 0.004) (table 2) and remained significant after removing the children with asthma or persistent wheeze from the analysis (parameter estimate = −0.0626, p = 0.025). Level of FEF_{25-75} (table 2) and FVC, adjusted for age, height, and sex, also tended to be lower among the hospitalized children, although not significantly so, particularly after exclusion of the children with asthma/persistent wheeze.

TABLE 2

REGRESSION EQUATIONS RELATING LEVEL OF LUNG FUNCTION TO HOSPITALIZATION FOR RESPIRATORY ILLNESS BEFORE ENTRY TO STUDY, AFTER ADJUSTMENT FOR AGE, HEIGHT, SEX, AND MATERNAL SMOKING

	ln FEV_1 (L) R-square = 0.60			ln FEF_{25-75} (L/s) R-square = 0.14		
Dependent Variables	Regression Coefficient	Standard Error	p Value	Regression Coefficient	Standard Error	p Value
Intercept	−6.1345	0.4062	0.0001	−4.5511	0.9386	0.0001
Age at entry, yr	0.0364	0.0064	0.0001	0.0208	0.0147	0.1581
Lung height at entry, inches	1.6234	0.1117	0.0001	1.3022	0.2581	0.0001
Sex at entry (1 = male)	−0.0622	0.0128	0.0001	−0.0054	0.0295	0.8545
Maternal smoking (1 = current)	−0.0149	0.0130	0.2548	−0.0768	0.0302	0.0114
Hospitalization (1 = yes)	−0.0654	0.0226	0.0040	−0.0962	0.0522	0.0662

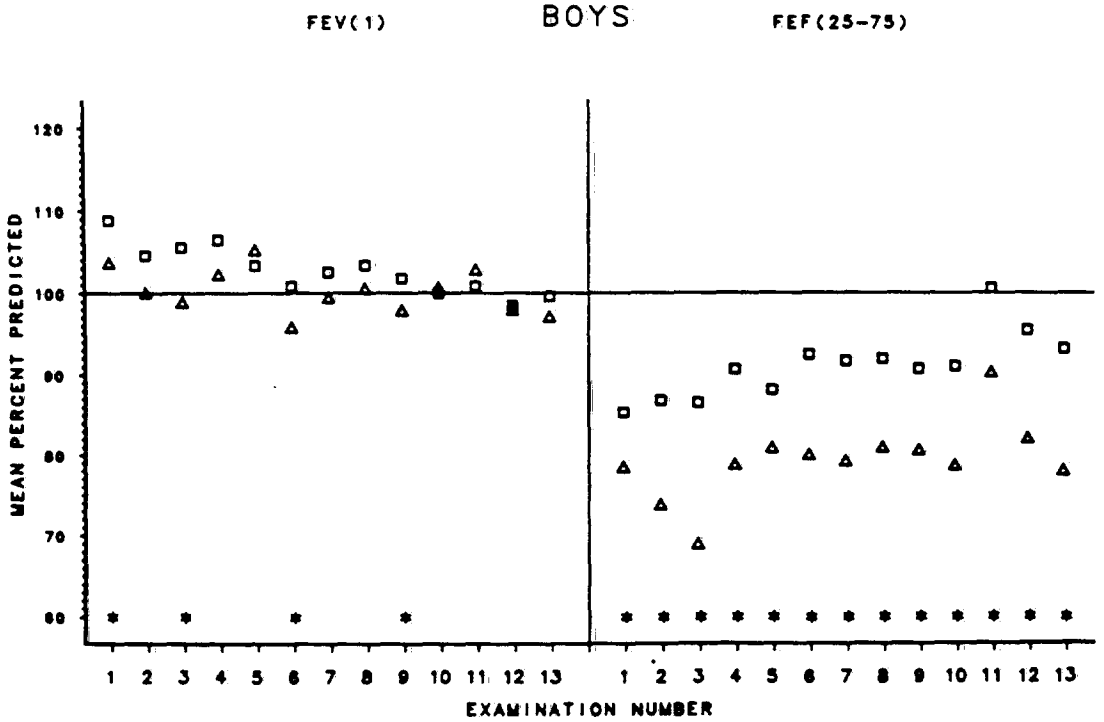

Fig. 3. Mean percent predicted FEV_1 and FEF_{25-75} at each annual examination (1 to 13) in boys (n = 422) classified according to presence or absence of history of hospitalization for respiratory illness prior to entry to study. Triangles = boys with history of hospitalization; squares = boys without history of hospitalization. The asterisks represent pairs of values ± 1 SE that do not overlap.

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TABLE 3

PARTIAL REGRESSION COEFFICIENTS REFLECTING RELATIONSHIPS BETWEEN CHANGES IN LEVEL OF LUNG FUNCTION OVER TIME AND OTHER COVARIATES*†

Dependent Variables	ln FEV_1 (L)			ln FEF_{25-75} (L/s)		
	Regression Coefficient	Standard Error	p Value	Regression Coefficient	Standard Error	p Value
Previous level of ln lung function	0.7341	0.0104	0.0001	0.7188	0.0107	0.0001
Maternal smoking (1 = current)	−0.0065	0.0028	0.0187	−0.0223	0.0054	0.0001
Personal smoking (1 = current)	−0.0102	0.0007	0.1207	−0.0230	0.0127	0.0712
Hospitalization (1 = yes)	−0.0104	0.0053	0.0503	−0.0359	0.0104	0.0006

* After adjustment for previous level of lung function, age, sex, height, age*change in height, and sex*height.
† Using the equation from Rosner and colleagues (8):

$$E(y_{i,t_0+\tau} - y_{i,t_0+\tau}) = \beta\Delta(1-\gamma)^t(1-\gamma),$$

the estimate of the ratio of the FEV_1 of the hospitalized child to the FEV_1 of the nonhospitalized child after one yr is exp (−0.0104) = 99.0%. The FEF_{25-75} of the hospitalized child to the FEF_{25-75} of the nonhospitalized child after one yr is exp (−0.0359) = 96.5%. These short-term projections assume that the children start at the same level of lung function and show the same growth in height over the 1-yr period.

In sex-stratified models, the associations between hospitalization and lower cross-sectional level of lung function, as described in the previous paragraph, were seen for boys but not for girls. Of the 69 children with a history of hospitalization at entry to the study, 60.9% were boys; there was a more equal proportion of boys and girls among those not hospitalized (table 4).

In the longitudinal analysis, after adjustment for "growth factors" and smoking, hospitalization was a significant predictor of change in level both of FEV_1 (parameter estimate = −0.0104, p = 0.05) and FEF_{25-75} (parameter estimate = −0.0359, p = 0.0006) (table 3), but not change in level of FVC. After additional adjustment for "ever diagnosis of asthma and current any wheeze," the association between a history of hospitalization and slower increase in forced expiratory volume remained significant. In a sex-stratified model, the association between hospitalization and slower increase in level of both FEV_1 (parameter estimate = −0.0134, p = 0.05) and FEF_{25-75} (parameter estimate = −0.0373, p = 0.004) remained significant for boys but not for girls, even after adjustment for "ever diagnosis of asthma and current any wheeze."

The smaller subgroup of children with both a history of hospitalization and a history of pneumonia prior to entry to the study (n = 17) was compared to the rest of the population. In the longitudinal analysis, the children had slower increase in level of FEF_{25-75} than the rest of the population after adjustment for "growth factors," smoking, and "ever asthma and current any wheeze" (parameter estimate for hospitalization and pneumonia = −0.0308, p = 0.03). In contrast to results for the larger group of children with a history of hospitalization, this negative association remained significant even after eliminating those with asthma/persistent wheeze at entry to the study.

Acute Lower Respiratory Illness as a Predictor of Subsequent Respiratory Symptoms

At entry to the study, when compared with children with no history of hospitalization for respiratory illness, children with a history of hospitalization had a higher prevalence of "any wheeze" (OR = 4.3; 95% CI = 2.4–7.5), persistent wheeze (OR = 5.3; 95% CI = 2.8–10.0), chronic cough (OR = 3.8; 95% CI = 2.0–7.2), and chronic phlegm (OR = 7.1; 95% CI = 2.8–18.2) (table 4). Over an eight-year period of follow-up, although the subjects with a history of previous hospitalization maintained a higher prevalence of "any wheeze," they had a steep reduction in the prevalence of symptoms of persistent wheeze, chronic cough, and chronic phlegm (table 4). The nonhospitalized group, on the other hand, developed an increasing prevalence of chronic cough and phlegm, predominantly among the smokers. Of those nonhospitalized children, smokers had 2.9 times as much chronic cough (95% CI = 1–8.2) and 10.9 times as much chronic phlegm (95% CI = 2.4–39.4) as the nonsmokers

TABLE 4

COMPARISON OF CHILDREN WITH AND WITHOUT HISTORY OF HOSPITALIZATION FOR RESPIRATORY ILLNESS PRIOR TO ENTRY TO THE STUDY

	Entry Year (t)		t+5		t+8	
Hospitalized	Yes	No	Yes	No	Yes	No
Number	69	731	40	546	31	460
Age (mean)	6.7	6.9	11.7	11.8	14.5	14.7
Sex						
Male, %	60.9	52.0	75.0	51.5	74.2	50.0
Female, %	39.1	48.0	25.0	48.5	25.8	49.5
Doctor's diagnosis of asthma at entry, %	30.4	4.2	32.5	4.4	29.0	5.2
Ever asthma, %	30.4	4.2	37.5	8.2	35.5	10.7
Persistent wheeze, %	27.5	6.7	2.5	0.7	0.0	0.9
Any wheeze, %	69.6	30.5	35.0	9.5	29.0	14.8
Chronic cough, %	24.6	7.9	0.0	1.5	0.0	4.4
Chronic phlegm, %	13.0	2.1	0.0	0.002	0.0	2.0
Bouts of cough/phlegm > 1 wk, %	56.5	28.0	1.0	5.2	9.7	11.5
Debilitating chest illness in past yr, %	60.9	26.8	1.0	2.7	6.5	4.1
Pneumonia before entry, %	55.1	9.4	47.5	10.0	54.8	10.0
Illness before age 2 yr, %	75.4	28.3	70.0	31.0	77.4	30.5
Maternal smoking, %	56.5	55.0	65.0	55.3	54.8	51.9
Personal smoking, %	0.0	0.0	0.0	3.1	0.0	16.5
FEV_1						
Mean % predicted	110.3	114.8	100.7	107.0	102.0	106.4
for nonwheezers, nonsmokers*					104.3 (n = 20)	107.0 (n = 282)
for smokers*						105.4 (n = 56)
FEF_{25-75}						
Mean % predicted	83.8	91.1	86.2	95.1	86.4	98.1
for nonwheezers, nonsmokers*					90.2 (n = 20)	100.5 (n = 282)
for smokers*						92.0 (n = 56)

* The number of children in these categories is smaller than the total number of children for whom symptom data is available because there were fewer children who successfully performed the forced expiratory maneuvers.

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(table 4). The previously hospitalized and nonhospitalized nonsmokers had a similarly low prevalence of chronic respiratory symptoms. Of note, 16.6% of the nonhospitalized children who were surveyed eight years after entry to the study had taken up smoking, whereas none of the hospitalized children had done so.

Discussion

For nonasthmatic children, report of pneumonia or hospitalization prior to this study were the strongest predictors of subsequent reduced level and growth of lung function. Many of the children with a history of LRI both in infancy and at school age had asthma or persistent wheeze by the time they entered the study. Children with ≥ 2 LRI in Study Year 2 did not have preexisting or subsequent lower level of lung function unless they also had a history of LRI before 2 yr of age. These data are consistent with the hypothesis that events in the prenatal period and in infancy may be more important determinants of lung function in later childhood than events in the school-age period.

To understand the detailed implications of the study, several of its limitations need to be addressed. Martinez and colleagues (11) have suggested that some infants have preexisting diminished pulmonary function that puts them at greater risk for acute wheezing LRI. In their study, preexisting diminished lung function was not a risk factor for LRI without wheeze. Our study design does not allow us to determine whether low lung function preceded LRI in infancy, or whether LRI in infancy preceded low lung function. Nor does it allow us to determine the role of wheeze in predicting the relationship between LRI and lung function in infancy. Our study was designed to examine the effect of LRI in the school-age years on subsequent lung function in asthmatic and nonasthmatic children. Although it has detailed prospective data on 5- to 11-yr-olds, it suffers from the potential for recall bias relating to early childhood illnesses. In this study we were unable to validate the reporting of hospitalization. It is unlikely, however, that parents would selectively recall previous hospitalization in sicker children because, regardless of subsequent events, early childhood hospitalization is usually experienced as a major event in family life.

As described above, loss to follow-up limits the age range within which this study can confidently make longitudinal projections. In addition, the estimates of the precision of these projections are limited because statistical techniques have not yet been developed for establishing confidence intervals around mean change in level of forced expiratory volumes for exposed and unexposed subjects. Because severe acute respiratory illness is a relatively rare event, this study also lacks the power to evaluate some aspects of the relationship between illness and level of lung function, particulary after stratifying by sex and controlling for asthma and smoking. Numbers of events are too small to explore potential interactions between passive smoking and previous hospitalization in their relationship to subsequent lung function. Since none of the previously hospitalized children with adequate smoking data took up smoking, this study cannot predict the extent to which these children would have been, as active smokers, at increased risk for lung function deficits. The lack of smoking in children previously hospitalized for respiratory illness may represent a "healthy smoker effect," where individuals who are constitutionally less comfortable smoking chose not to take up the habit.

Our study supports the observations of others that males appear to be more at risk for respiratory illness in infancy than females. The Tecumseh and Chapel Hill studies have noted the excess of LRI among male infants, but not among 5- to 11-yr-old boys as compared to girls (12–14). Taussig (15) has suggested that the early LRI in male subjects may reflect the preponderance of males with smaller airways for lung size (referred to as dysynapsis by Green and Mead [16, 17]), and that the equalizing of sex-specific LRI rates in school-age children may coincide with the growth spurt during which males acquire an airway size/lung size ratio similar to that present in females.

Martin and colleagues (18) suggest that in the adolescent years male asthmatics appear to improve more than female asthmatics. In our study, male subjects with illness before 2 yr of age and ≥ 2 LRI at Study Year 2, half of whom were asthmatic, did not appear to catch up to their peers (asthmatics or nonasthmatics) in the adolescent years. They had a slower increase in level of FEF_{25-75} than the rest of the cohort, and a faster increase in level of FVC, which at entry to the study was equal to or higher than the mean FVC in the rest of the cohort. This would support an association between dysynapsis, male sex, an early history of asthma, and frequent LRI in childhood as well as in infancy.

Cross-sectional modeling suggests that for nonasthmatic subjects, previous hospitalization for acute respiratory illness is independent of the effect of passive smoking, associated with a deficit in FEV_1 at entry to the study. The model predicts that a nonasthmatic 7-yr-old boy with no passive smoking experience, but with previous hospitalization for respiratory illness, would have a 6.1% lower level of FEV_1 than a nonasthmatic boy with neither hospitalization nor passive smoking experience. The model (table 2) also predicts that passive smoking together with hospitalization would be associated with a 7.5% deficit.

The sex-stratified longitudinal model that includes all boys suggests that if two hypothetical 6-yr-old boys, one with a history of hospitalization and one without such a history, started at the median height and FEV_1 for their age, then eight years later the boy with a history of hospitalization would have an FEV_1 that was 5.0% lower, and an FEF_{25-75} that was 11.7% lower than that of the boy without a history of hospitalization, assuming all other factors affecting growth were equal and the boys were neither exposed to smoking nor had wheeze symptoms in the years subsequent to entry to the study. The projection also assumes that the parameter estimate is applicable over the 8-yr period.

Nonwheezing boys with no smoking exposure, but with *both* previous hospitalization and pneumonia, would, after eight years, have an FEF_{25-75} that was 11.8% lower than other nonwheezing boys without hospitalization and pneumonia, projecting from a model that excludes those with history of asthma or symptoms of persistent wheeze at entry to the study. The East Boston study follows children at least into the mid-teens, but since lung growth may continue into the late teens and early twenties, more follow-up time is needed to determine whether or not those children identified as persisting at lower levels of function as teenagers remain impaired as adults, and is the group of nonsmokers at greatest risk of developing chronic obstructive lung disease.

Although this study found associations between early childhood acute respiratory illness and subsequent development of chronic respiratory symptoms and cough at entry to the study, there

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were no effects that were maintained over a period of eight years in nonsmokers. Personal smoking was the overwhelming predictor of subsequent cough and phlegm, and none of the children who reported previous hospitalization prior to study onset took up smoking. These results differ from the results of the large prospective study of children in the United Kingdom reported by Kiernan, Colley and colleagues (19), which found long-term effects of childhood respiratory illness on the long-term development of chronic cough. An interaction between higher air pollution levels in the United Kingdom and the effect of early childhood illness may account for the difference in the relationship between early illness and subsequent symptoms in the cohort in East Boston as compared to the cohort in the United Kingdom (20, 21). Studies of respiratory morbidity and mortality in other populations of children may enable us to explore the interaction between severe respiratory illness in early childhood and the effect of other exposures such as cigarette smoke and indoor or outdoor air pollution.

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